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Upper limb motor rehabilitation impacts white matter microstructure in multiple sclerosis

Laura Bonzano [a,b,*], Andrea Tacchino [c], Giampaolo Brichetto [c], Luca Roccatagliata [b,d], Adriano Dessypris [a,e], Paola Feraco [a], Maria L. Lopes De Carvalho [f], Mario A. Battaglia [g], Giovanni L. Mancardi [a,b], Marco Bove [e,**]

[a] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy
[b] Magnetic Resonance Research Centre on Nervous System Diseases, University of Genoa, Genoa, Italy
[c] Scientific Research Area, Italian Multiple Sclerosis Foundation (FISM), Genoa, Italy
[d] Department of Health Sciences, Biostatistics Unit, University of Genoa, Genoa, Italy
[e] Department of Experimental Medicine, Section of Human Physiology and Centro Polifunzionale di Scienze Motorie, University of Genoa, Genoa, Italy
[f] AISM Rehabilitation Service, Italian Multiple Sclerosis Society, Genoa, Italy
[g] Department of Physiopathology, Experimental Medicine and Public Health, University of Siena, Siena, Italy

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ABSTRACT

Upper limb impairments can occur in patients with multiple sclerosis, affecting daily living activities; however there is at present no definite agreement on the best rehabilitation treatment strategy to pursue. Moreover, motor training has been shown to induce changes in white matter architecture in healthy subjects.

This study aimed at evaluating the motor behavioral and white matter microstructural changes following a 2-month upper limb motor rehabilitation treatment based on task-oriented exercises in patients with multiple sclerosis.

Thirty patients (18 females and 12 males; age = 43.3 ± 8.7 years) in a stable phase of the disease presenting with mild or moderate upper limb sensorimotor deficits were randomized into two groups of 15 patients each. Both groups underwent twenty 1-hour treatment sessions, three times a week. The "treatment group" received an active motor rehabilitation treatment, based on voluntary exercises including task-oriented exercises, while the "control group" underwent passive mobilization of the shoulder, elbow, wrist and fingers.

Before and after the rehabilitation protocols, motor performance was evaluated in all patients with standard tests. Additionally, finger motor performance accuracy was assessed by an engineered glove.

In the same sessions, every patient underwent diffusion tensor imaging to obtain parametric maps of fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. The mean value of each parameter was separately calculated within regions of interest including the fiber bundles connecting brain areas involved in voluntary movement control: the corpus callosum, the corticospinal tracts and the superior longitudinal fasciculi.

The two rehabilitation protocols induced similar effects on unimanual motor performance, but the bimanual coordination task revealed that the residual coordination abilities were maintained in the treated patients while they significantly worsened in the control group ($p = 0.002$). Further, in the treatment group white matter integrity in the corpus callosum and corticospinal tracts was preserved while a microstructural integrity worsening was found in the control group (fractional anisotropy of the corpus callosum and corticospinal tracts: $p = 0.033$ and $p = 0.022$; radial diffusivity of the corpus callosum and corticospinal tracts: $p = 0.004$ and $p = 0.008$). Conversely, a significant increase of radial diffusivity was observed in the superior longitudinal fasciculi in both groups ($p = 0.02$), indicating lack of treatment effects on this structure, showing damage progression likely due to a demyelination process.

All these findings indicate the importance of administering, when possible, a rehabilitation treatment consisting of voluntary movements. We also demonstrated that the beneficial effects of a rehabilitation treatment are task-dependent and selective in their target; this becomes crucial towards the implementation of tailored rehabilitative approaches.

* Correspondence to: L. Bonzano, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Largo Daneo 3 (ex via De Toni 5), 16132 Genoa, Italy. Fax: +39 0103538639.
** Correspondence to: M. Bove, Department of Experimental Medicine, Section of Human Physiology, Viale Benedetto XV 3, 16132 Genoa, Italy. Fax: +39 0103538194.
E-mail addresses: laura.bonzano@unige.it (L. Bonzano), marco.bove@unige.it (M. Bove).

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Introduction

Impaired sensorimotor function is frequent in multiple sclerosis (MS). Sensorimotor impairments of the lower limbs affecting mobility are reported in 75% of patients with MS (PwMS), whereas dysfunctions of the upper limbs occur in 66% of PwMS (Johansson et al., 2007; Spooren et al., 2012). The level of arm and hand functioning greatly defines the ability to perform daily living activities like eating, dressing, and grooming (Yozbatiran et al., 2006).

Neurorehabilitation is targeted at maintaining and possibly improving the residual capacities of neurological patients with the aim to preserve their personal and social activities, and it constitutes an important part of quality health care in PwMS. There is at present no definite agreement on which specific exercise therapy program can be considered the most successful in improving activities and participation. Different training programs have been employed for upper limb neurorehabilitation, ranging from more traditional strategies to newer techniques emphasizing the learning and practice of functional motor skills within a "task-specific" context (Solari et al., 1999; Spooren et al., 2012). In addition, it has been proposed that a training based on the performance of voluntary movements showed significant improvements in motor performance in healthy subjects with respect to passive training (Bayona et al., 2005; Lotze et al., 2003). Further, active training has been found to induce more prominent increases in fMRI activation of the contralateral primary motor cortex (M1), corticospinal excitability and intracortical facilitation than passive training (Lotze et al., 2003). All these findings suggest the important role for voluntary drive in motor learning and neurorehabilitation. In agreement with this notion, voluntary exercise has been convincingly shown to attenuate the clinical deficits and the underlying neuropathological process in animal models of neurodegenerative disorders (Ang and Gomez-Pinilla, 2007; Cotman and Berchtold, 2002; Cotman et al., 2007; Kramer and Erickson, 2007; Rossi et al., 2009).

Recently, changes in white matter (WM) architecture have been observed in healthy subjects after motor training (Draganski and May, 2008; Scholz et al., 2009; Taubert et al., 2010). WM fiber pathways form the brain communication network; thus, the physical condition of a given pathway can determine the efficiency of signal transmissions between brain regions and might thereby influence behaviors relying on that pathway (Fields, 2008; Johansen-Berg, 2010; Johansen-Berg et al., 2010; Scholz et al., 2009). In this framework, the increasing sensorimotor impairment observed in PwMS over the disease course could be mainly due to the progression of WM damage, that is present in these patients since the early stages (Evangelou et al., 2000; Ferguson et al., 1997; Ge et al., 2005; van Waesberghe et al., 1999). In particular, reductions in the microstructural integrity of the corpus callosum (CC) have been shown to be associated with decreased sensorimotor performance, impairment in visuomotor learning and deficit in bimanual coordination (Bonzano et al., 2008, 2011a,b; Larson et al., 2002; Pelletier et al., 1992).

The present study was designed to evaluate the motor behavioral and WM microstructural architecture changes, with a focus on the WM fiber bundles connecting brain areas involved in voluntary movement control, following a 2-month upper limb motor rehabilitation treatment including task-oriented exercises in PwMS.

Material and methods

Patients

Thirty right-handed PwMS in a stable phase of the disease presenting with mild or moderate sensorimotor deficit in one or both upper limbs were recruited for this study. The Medical Research Council (MRC) scale (0 to 5 grades) was adopted for testing muscle strength at the proximal (i.e., shoulder and elbow) and distal (i.e., wrist and fingers) segments (Compston, 2010). Inclusion criteria were the following MRC scores of patient's effort: grade 4 in all muscle groups or grade 3 in no more than two joints (mild deficit), or grade 3 in all muscle groups (moderate deficit). We excluded patients with relapses and steroid-use or a worsening of the Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983) in the last three months, psychiatric disorders and severe cognitive impairment.

Among the included patients (18 females and 12 males; mean age $= 43.3 \pm 8.7$ years) 22 were affected by a relapsing–remitting and 8 by a secondary progressive form of MS. Demographic and clinical characteristics of the patients are reported in Table 1.

The study was approved by the ethical committee of our institution and the patients' consent was obtained according to the Declaration of Helsinki.

Rehabilitative protocols

We were interested in investigating the effects of an active upper limb rehabilitation treatment based on volitional tasks on motor performance and white matter microstructure. To this aim, we defined a "control treatment", as strongly suggested in a recent critical review of studies assessing structural plasticity following training (Thomas and Baker, 2013). In fact, comparing two groups who have been trained on different tasks allows showing that potential changes are specific to a given task and not a general effect of any training. Therefore, the 30 recruited PwMS were randomly assigned to two groups, with the use of a computer-generated schedule: one receiving an active motor rehabilitation treatment ("treatment group"—15 patients) and one receiving a passive motor rehabilitation treatment ("control group"—15 patients) (Table 1).

The two rehabilitative protocols were designed with the intention that all the patients were similarly invested in the study by equating patients' overall experience thus limiting possible biases (Thomas and Baker, 2013); both groups of patients underwent twenty 1-hour treatment sessions, three times a week, at AISM Rehabilitation Centre, Italian Multiple Sclerosis Society, Genoa, Italy.

In details, the patients assigned to the treatment group were rehabilitated with an active protocol based on voluntary exercises for neuromuscular control to improve proprioceptive sensibility, muscle strength, stability and coordination of the upper limbs, mainly including task-oriented exercises with the goal to improve activities of daily living (Nelson, 1996). The first 5 sessions of the rehabilitative protocol were focused on voluntary exercises executed unilaterally with the right and left upper limbs (60% of treatment time). This part of the treatment dealt with both non task-oriented exercises, such as grasping wooden cubes of different sizes, pinching, reaching a target displayed in front of the patient, and task-oriented exercises such as ironing a shirt and putting a dish in a draining board. In the last 40% of the treatment, bimanual task-oriented exercises, such as sewing, doing patchwork and paper mandala, cooking, sweeping, and screwing a cap on a bottle, were administered to the patients. Gradually, from the 6th to the 12th sessions, the percentage of bimanual task-oriented exercises increased to reach 100% in the last 5 sessions. Thus, unimanual and bimanual voluntary exercises were differently weighted in each session along the rehabilitative program (sessions 1–5: 60%–40%, respectively; sessions 6–10: 40%–60%, respectively; sessions 11–15: 20%–80%, respectively; and sessions 16–20: 0%–100%, respectively).

The control group only performed tasks without detectable muscle activity, through passive mobilization of the shoulder, elbow, wrist and fingers delivered by a physical therapist. Analogously, in the passive rehabilitation protocol the percentage of unimanual and bimanual passive mobilizations delivered by the therapist followed the scheme used for the "treatment group" (i.e., sessions 1–5: 60%–40%, respectively; sessions 6–10: 40%–60%, respectively; sessions 11–15: 20%–80%, respectively; and sessions 16–20: 0%–100%, respectively).

Table 1
Demographic and clinical characteristics of the patients included in the two groups: the "treatment group" received an active motor rehabilitation treatment including task-oriented exercises, the "control group" received a passive motor rehabilitation treatment, based on upper limb mobilization techniques performed by a physical therapist.

Group	ID	Age (years)	Gender	MS phenotype	EDSS at baseline	Disease duration (months)	Time from last relapse before treatment (months)	Disease-modifying therapy	Affected upper limb	Severity of motor deficit
Treatment	1	35	F	RR	4	62	5	Immunosuppressant	Left	Mild
	2	56	M	SP	4	148	11	Immunosuppressant	Right	Mild
	3	35	F	RR	5.5	115	4	Immunosuppressant	Right	Mild
	4	47	M	SP	4.5	84	>12	None	Bilateral	Moderate
	5	39	F	RR	2	52	>12	Immunomodulant	Right	Mild
	6	33	F	RR	4.5	88	>12	None	Left	Mild
	7	31	F	RR	3	64	11	Immunosuppressant	Bilateral	Mild
	8	51	M	SP	6	88	>12	Immunosuppressant	Left	Mild
	9	49	M	SP	6	100	>12	None	Left	Mild
	10	47	M	RR	3	110	>12	none	Right	Mild
	11	59	F	RR	4	160	>12	immunomodulant	Bilateral	Mild
	12	47	F	RR	4.5	188	>12	None	Bilateral	Mild
	13	43	F	RR	6.5	22	>12	Immunomodulant	Left	Mild
	14	30	F	RR	5	120	6	Immunosuppressant	Bilateral	Mild
	15	49	F	RR	3	234	9	None	Bilateral	Mild
	Mean (SD)	43.4 (9.1)			4.4 (1.3)	109.0 (55.3)				
Control	1	33	F	RR	5.5	28	>12	None	Left	Mild
	2	35	F	RR	4.5	60	6	Immunosuppressant	Right	Mild
	3	56	M	SP	5	139	>12	Immunosuppressant	Left	Mild
	4	31	F	RR	3	49	>12	Immunosuppressant	Right	Mild
	5	35	F	RR	4.5	112	5	Immunomodulant	Right	Mild
	6	33	F	RR	4	81	10	None	Left	Mild
	7	49	M	SP	6	78	>12	Immunosuppressant	Right	Mild
	8	49	M	SP	5.5	91	>12	None	Bilateral	Mild
	9	38	M	RR	4.5	60	>12	Immunomodulant	Right	Mild
	10	47	M	RR	3.5	102	11	None	Right	Mild
	11	55	F	RR	4	354	>12	None	Left	Mild
	12	50	F	RR	3.5	241	5	Immunomodulant	Left	Mild
	13	39	F	RR	2.5	42	10	Immunomodulant	Right	Mild
	14	47	M	RR	3	79	>12	Immunosuppressant	Bilateral	Mild
	15	51	M	SP	6	81	7	Immunosuppressant	Bilateral	Mild
	Mean (SD)	43.2 (8.6)			4.3 (1.1)	106.5 (85.2)				

RR = relapsing–remitting; SP = secondary progressive.

Motor performance evaluation

Before ("PRE session", i.e., baseline) and after ("POST session") the rehabilitation treatment, motor performance was evaluated in all the patients for both arms with the following standard measures of global disability and sensorimotor dysfunction: upper limb motor functions by the Action Research Arm Test (ARAT) (Lyle, 1981), hand dexterity by the nine Hole Peg Test (9-HPT) (Fischer et al., 1999), and grip strength by a dynamometer (GRIP).

In addition, an engineered glove was used to quantify finger motor performance accuracy; this simple and objective method has been recently demonstrated to be able to discriminate healthy controls and PwMS even with very low disability (Bonzano et al., 2013). Specifically, patients were asked to perform with their eyes closed repetitive finger opposition movements of thumb to index, medium, ring and little fingers, with the dominant hand (right for all the patients) at their spontaneous and maximal velocity. The finger motor sequence was repeated with both hands simultaneously and paced with a metronome tone set at a rate of 2 Hz, to assess bimanual coordination. From the raw data recorded by the glove system, different parameters were then extracted: the movement rate at spontaneous (RATE-SV) and maximum velocity (RATE-MV) conditions. When the task was performed with the two hands, the inter hand interval (IHI) was calculated as index of bimanual coordination: the larger the IHI value, the more severe the impairment in bimanual coordination (Bonzano et al., 2008).

Conventional MRI

Axial dual-echo proton density (PD)/T2-weighted images (slice thickness: 4 mm; TR: 2500 ms; TE: 25.5/127.4 ms; flip angle: 90°; FOV: 250 mm; matrix: 256 × 256) were acquired to detect T2 lesions. Particularly, two observers, blinded to the clinical data and rehabilitative protocol, identified hyperintense lesions on PD/T2-weighted scans and checked for each patient whether he/she developed new T2 lesions during the study period, by comparing the POST scan with the PRE scan.

Diffusion tensor imaging

Before ("PRE session", i.e., baseline) and after ("POST session") the rehabilitation protocol, every patient underwent a magnetic resonance imaging examination on a 1.5-Tesla scanner (Signa Excite General Electric, WI), including the acquisition of axial single-shot spin-echo echo-planar diffusion tensor imaging (DTI) (slice thickness: 2 mm; TR: 16,000 ms; TE: 105 ms; flip angle: 90°; field of view (FOV): 240 mm; matrix: 128 × 128 interpolated during reconstruction to 256 × 256; number of excitations (NEX): 2), with diffusion gradients applied in 15 noncollinear directions ($b = 1000$ s/mm^2) and two baseline acquisitions without diffusion gradients (b0 images).

DTI data were processed by using the FMRIB's Diffusion Toolbox, FDT (Smith et al., 2004). After correction for eddy current distortions and motion artifacts, a diffusion tensor model was fitted at each voxel and the three eigenvalues (λ_1, λ_2, and λ_3) were calculated; hence, DTI-derived parametric maps were obtained (Basser, 1995; Basser and Pierpaoli, 1996). Particularly, for each patient and for each study session, in order to investigate white matter microstructural integrity we analyzed fractional anisotropy (FA), axial diffusivity ($\lambda_{\parallel}$), i.e., the water diffusivity parallel to the axonal fibers, represented by λ_1, radial diffusivity ($\lambda_{\perp}$), i.e., the water diffusivity perpendicular to the axonal fibers, obtained as the average of λ_2 and λ_3 (Song et al., 2002), and mean diffusivity (MD).

All the obtained parametric maps were nonlinearly transformed and aligned to 1 × 1 × 1 mm standard space according to the TBSS routines (Smith et al., 2006). We created some regions of interest (ROIs) from the JHU ICBM 81 white matter labels atlas included in FSL (Mori et al., 2005), visually checked the location of each ROI on each map and calculated the mean value of the different DTI metrics in each ROI. In details, different masks were selected, including the WM fiber bundles connecting brain areas involved in voluntary movement control, i.e., the corpus callosum (CC), the left and right corticospinal tract (CST) and the left and right superior longitudinal fasciculus (SLF) (Fig. 1). Indeed, CC pathology occurs in MS since the early disease phase (Evangelou et al., 2000; Ge et al., 2004), and CC abnormalities have been related to decreased sensorimotor performance, impairment in visuomotor learning and deficit in bimanual coordination (Bonzano et al., 2008, 2011a,b; Larson et al., 2002; Pelletier et al., 1993). CST abnormalities can be associated with weakness in MS (Reich et al., 2008), spasticity, deficits in executing fine movements and in motor control of the limbs. The SLF allows the integration of motor and decision-making centers with visual and sensory ones; it can be damaged in MS (Bonzano et al., 2009) and could affect grasping actions, movement preparation and planning (Jang and Hong, 2012; Koch et al., 2010).

Furthermore, we calculated the white matter signal-to-noise ratio (SNR) by measuring the SNR within each ROI, for each scan of each patient, with the method proposed by Price et al. (1990), which estimates the noise from the subtraction of two sequentially acquired images. In details, we subtracted the second b0 image from the first one obtaining a measure of the random noise introduced by the scanner itself ("noise image") and we calculated the SNR by the formula:

$$\mathrm{SNR}_{\mathrm{ROI}} = \sqrt{2}\frac{\overline{S}_{\mathrm{ROI}}}{\sigma_{\mathrm{ROI}}(N)}$$

where $\overline{S}_{\mathrm{ROI}}$ is the mean signal intensity of the first b0 image within the selected ROI and $\sigma_{\mathrm{ROI}}(N)$ is the standard deviation of the voxel values of the noise image in the same ROI.

Statistics

First, to evaluate differences in the initial motor performance and white matter microstructural integrity between the two groups of PwMS (treatment group vs. control group), ANOVA was separately performed on all the motor performance and DTI-derived parameters collected at baseline (PRE session).

To evaluate a possible change in SNR between the two sessions (POST session vs. PRE session) a paired *t*-test was performed for each analyzed ROI. Then, to assess the effects of the active rehabilitation treatment and the passive mobilization protocol, the obtained measurements were compared between the two sessions (POST session vs. PRE session) and the two groups (treatment group vs. control group) by means of factorial ANOVA with repeated measures (RM-ANOVA), with TIME (PRE and POST) as within-subject factor and GROUP (treatment and control) as between-subject factor. When the task had to be performed with the two hands separately (ARAT, 9-HPT and GRIP) the factor HAND (left and right) was considered as within-subject factor.

In addition, for the DTI-derived parameters (FA, $\lambda_{\parallel}$, $\lambda_{\perp}$ and MD) the factor HEMISPHERE (left and right) was taken into account as a within-subject factor when analyzing the left and right CST and SLF fiber bundles.

Significant main effects were explored with the Newman–Keuls post-hoc test.

Results

Motor performance

At baseline (PRE session), motor performance standard tests showed no difference between the treatment and the control group for both hands (ARAT: $F(1,56) = 0.23$, $p = 0.63$; 9-HPT: $F(1,56) = 0.30$, $p = 0.58$; GRIP: $F(1,56) = 1.02$, $p = 0.32$). Also, finger opposition movement performance with the right hand and bimanual coordination did not differ between the two groups (RATE-SV: $F(1,28) = 0.13$, $p = 0.72$; RATE-MV: $F(1,28) = 0.08$, $p = 0.78$; IHI: $F(1,28) = 0.97$, $p = 0.33$).

The active rehabilitation treatment and the passive mobilization protocol induced similar effects on unimanual motor performance. Indeed, on average, a statistically significant improvement as effect of TIME was found in ARAT score ($F(1,56) = 5.53$, $p = 0.022$), average time to complete the 9-HPT ($F(1,56) = 27.59$, $p < 0.000001$), GRIP strength ($F(1,56) = 11.40$, $p = 0.0013$), and RATE-MV ($F(1,28) = 6.32$, $p = 0.018$), while no change was observed in RATE-SV ($F(1,28) = 0.56$, $p = 0.46$). The similar trend between the groups was underlined by the lack of TIME × GROUP interaction (ARAT: $F(1,56) = 0.44$, $p = 0.51$; 9-HPT: $F(1,56) = 0.0008$, $p = 0.98$; GRIP: $F(1,56) = 0.01$, $p = 0.92$, RATE-SV: $F(1,28) = 0.0003$, $p = 0.98$; RATE-MV: $F(1,28) = 1.39$, $p = 0.25$). As we found no significant difference in treatment-induced motor performance improvements between the two hands, the results are reported as an average on the data collected for the two hands (Figs. 2A–E).

A significant change, as effect of TIME, was found in IHI after treatment ($F(1,28) = 7.66$, $p = 0.001$). However, differently from the other motor performance parameters, in the bimanual coordination task there was a significant difference between the treatment and the control group, as indicated by the significant interaction TIME × GROUP (IHI: $F(1,28) = 8.40$, $p = 0.007$) (Fig. 2F). In fact, IHI remained stable after the rehabilitation program in the treatment group, indicating a maintenance of the coordination abilities in the treated patients, but significantly increased in the control group ($p = 0.002$), demonstrating a worsening in bimanual coordination in these patients.

On the other hand, no patient showed any change in EDSS score after treatment. No patient had a relapse during the study.

Conventional MRI

We found that one patient belonging to the control group showed a new T2 lesion in the right cerebral peduncle (included in our mask of

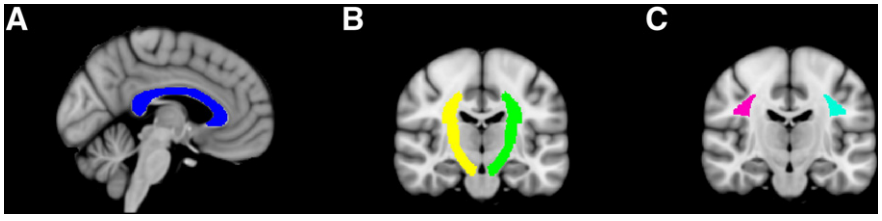

Fig. 1. Regions of interest (ROIs) selected to investigate the microstructural integrity of the white matter fiber bundles connecting brain areas involved in voluntary movement control. (A) Corpus callosum (CC). (B) Left and right corticospinal tract (CST). (C) Left and right superior longitudinal fasciculus (SLF).

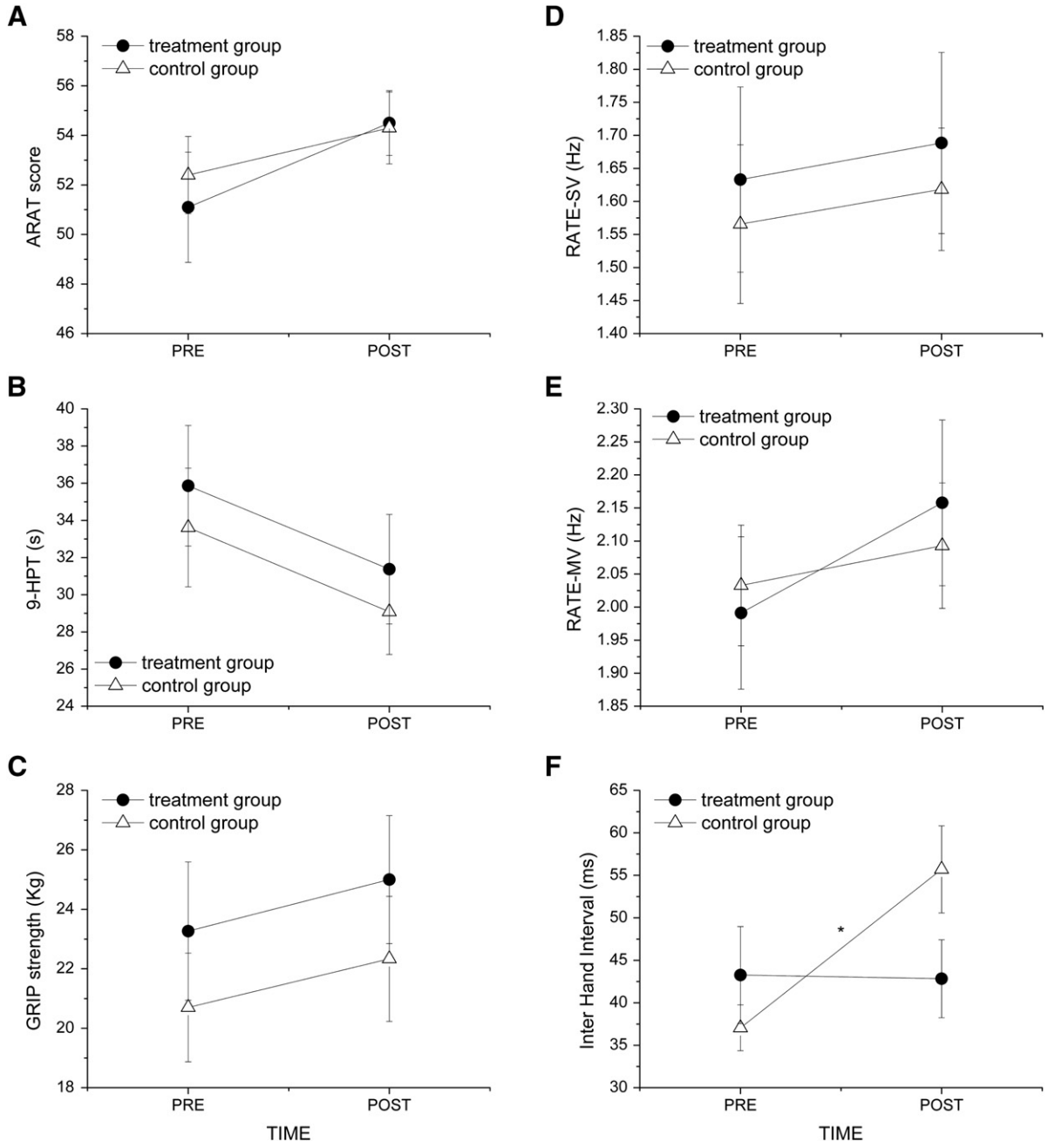

Fig. 2. Motor performance parameters (mean ± s. e.) measured at the different tests for the two groups (treatment and control) in the two sessions, before (PRE) and after (POST) the rehabilitation treatment. (A) Score obtained at the Action Research Arm Test (ARAT score). (B) Time to complete the nine Hole Peg Test (9-HPT). (**C**) Hand grip strength assessed with a dynamometer (GRIP strength). (D) Movement rate (i.e., number of finger taps per second) in the spontaneous velocity condition (RATE-SV). (E) Movement rate in the maximum velocity condition (RATE-MV). (F) Inter hand interval (IHI). Higher values indicate greater impairment in bimanual coordination. (**A–C**) The reported values are the average of the two hands. * indicates statistical significance.

the corticospinal tract), while one patient belonging to the treatment group showed an enlarging T2 lesion in the anterior corpus callosum.

DTI—signal-to-noise ratio

No significant change in SNR was observed at the POST session scan with respect to baseline (CC, PRE: 18.42 ± 4.02, POST: 18.75 ± 4.06; df = 29, t = 0.38, p = 0.71. CST, PRE: 18.56 ± 4.02, POST: 18.80 ± 4.90; df = 29, t = 0.31, p = 0.76. SLF, PRE: 18.63 ± 3.43, POST: 18.56 ± 3.28; df = 29, t = 0.14, p = 0.89). DTI-parameter maps of diffusion direction color-encoded FA, axial and radial diffusivities for a representative subject are shown in Fig. 3.

DTI—fractional anisotropy

At baseline, white matter structural integrity, evaluated by FA, was similar in the two groups for all the investigated ROIs (CC: $F(1,28) = 0.051$, $p = 0.82$; CST_left: $F(1,28) = 0.62$, $p = 0.44$; CST_right: $F(1,28) = 0.81$, $p = 0.38$; SLF_left: $F(1,28) = 0.53$, $p = 0.47$; SLF_right: $F(1,28) = 2.20$, $p = 0.15$).

After 2 months, FA values were found to be slightly but not significantly different with respect to baseline (effect of TIME) in the CC and bilaterally in the CST in the two groups of patients (CC: $F(1,28) = 2.24$, $p = 0.15$; CST: $F(1,56) = 2.86$, $p = 0.096$). However, the significant interaction TIME × GROUP (CC: $F(1,28) = 5.12$, $p = 0.03$; CST:

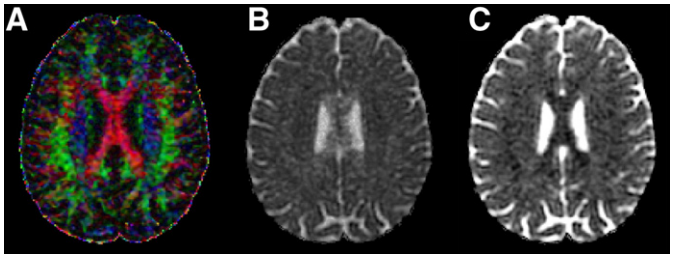

Fig. 3. DTI-parameter maps of an axial slice at the level of the corpus callosum for a representative subject. (A) Diffusion direction color-encoded fractional anisotropy. (B) Axial diffusivity. (C) Radial diffusivity.

$F(1,56) = 10.66$, $p = 0.0019$) indicated that this trend was different between the two groups. Post-hoc analysis showed that FA values in both the CC and CST after passive mobilization were significantly lower than those measured at baseline in the same group, indicating damage progression in the control group (CC: $p = 0.033$; CST: $p = 0.022$). Conversely, no significant change in the CC FA was observed in the treatment group; only a slight but not significant increase in the CST FA was found after the treatment (Figs. 4A and B). It should be noted that a similar effect of the treatment was observed on the left and right CST as shown by the lack of interaction TIME × GROUP × HEMISPHERE ($F(1,56) = 0.025$, $p = 0.88$). For this reason, data in the graph represent the average on the left and right CST (Fig. 4B). Finally, no significant FA change with respect to baseline was observed in the SLF of both hemispheres in both groups indicating no effect of either passive mobilization or treatment on this brain structure ($F(1,56) = 2.51$, $p = 0.12$) (Fig. 4C).

DTI—axial diffusivity

At baseline, $\lambda_{\parallel}$ was similar in the two groups for all the investigated ROIs (CC: $F(1,28) = 0.58$, $p = 0.45$; CST_left: $F(1,28) = 0.93$, $p = 0.34$; CST_right: $F(1,28) = 0.26$, $p = 0.61$; SLF_left: $F(1,28) = 0.11$, $p = 0.74$; SLF_right: $F(1,28) = 0.02$, $p = 0.88$).

No significant change in $\lambda_{\parallel}$ was observed in the investigated ROIs after both the treatment and passive mobilization, as indicated by the lack of TIME effect (CC: $F(1,28) = 0.09$, $p = 0.77$; CST: $F(1,56) = 0.07$, $p = 0.79$; SLF: $F(1,56) = 1.41$, $p = 0.24$) and of interaction TIME × GROUP (CC: $F(1,28) = 0.57$, $p = 0.46$; CST: $F(1,56) = 2.31$, $p = 0.13$; SLF: $F(1,56) = 0.005$, $p = 0.94$) (Figs. 5A–C).

DTI—radial diffusivity

At baseline, $\lambda_{\perp}$ was similar in the two groups for all the investigated ROIs (CC: $F(1,28) = 0.23$, $p = 0.63$; CST_left: $F(1,28) = 0.01$, $p = 0.90$; CST_right: $F(1,28) = 0.14$, $p = 0.71$; SLF_left: $F(1,28) = 0.13$, $p = 0.72$; SLF_right: $F(1,28) = 0.02$, $p = 0.90$).

On average, a significant effect of TIME on $\lambda_{\perp}$ was observed in the CC ($F(1,28) = 7.02$, $p = 0.01$) while only a slight but not significant effect was observed in the CST ($F(1,56) = 3.64$, $p = 0.06$). However, a different trend between the two groups in the CC and CST fiber bundles was indicated by the TIME × GROUP interaction (CC: $F(1,28) = 7.33$, $p = 0.01$; CST: $F(1,56) = 6.19$, $p = 0.01$). Post-hoc analysis showed a significant increase in $\lambda_{\perp}$ in the CC and CST in the control group after 2 months of passive mobilization (CC: $p = 0.004$; CST: $p = 0.008$) while no change was observed at POST in the treatment group with respect to baseline (CC: $p = 0.97$; CST: $p = 0.91$) (Figs. 5D and E).

Concerning the SLF, on average, a significant increase of $\lambda_{\perp}$ was observed with respect to baseline (effect of TIME) ($F(1,56) = 5.85$, $p = 0.02$). Further, we found no significant TIME × GROUP interaction indicating a similar trend for $\lambda_{\perp}$ change between the two groups ($F(1,56) = 1.41$, $p = 0.24$) (Fig. 5F).

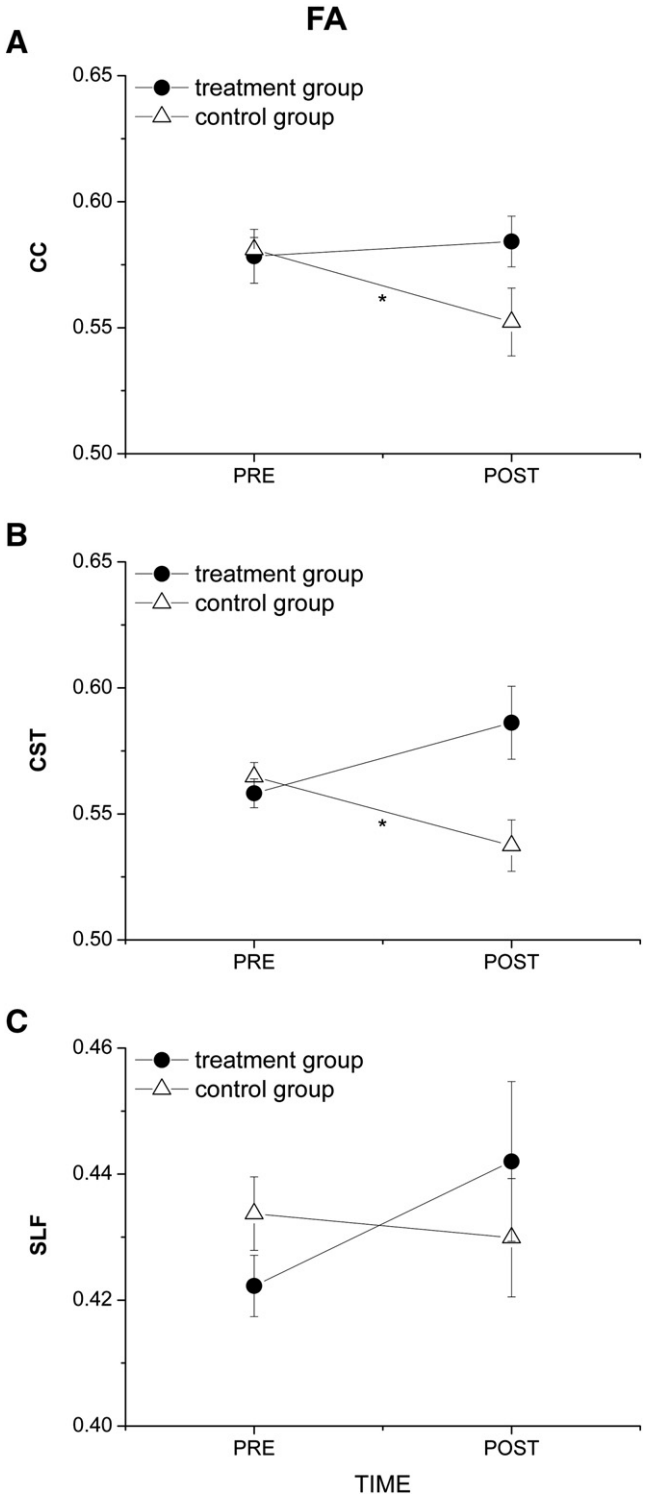

Fig. 4. Fractional anisotropy (FA) values (mean ± s. e.) within the selected ROIs in the two groups of patients (treatment and control) before (PRE) and after (POST) the rehabilitation treatment. (A) Corpus callosum (CC). (B) Corticospinal tract (average on the left and right CST). (C) Superior longitudinal fasciculus (average on the left and right SLF). * indicates statistical significance.

DTI—mean diffusivity

At baseline, MD was similar in the two groups for all the investigated ROIs (CC: $F(1,28) = 0.4$, $p = 0.53$; CST_left: $F(1,28) = 0.36$, $p = 0.56$; CST_right: $F(1,28) = 0.0026$, $p = 0.96$; SLF_left: $F(1,28) = 0.15$, $p = 0.70$; SLF_right: $F(1,28) = 0.26$, $p = 0.87$).

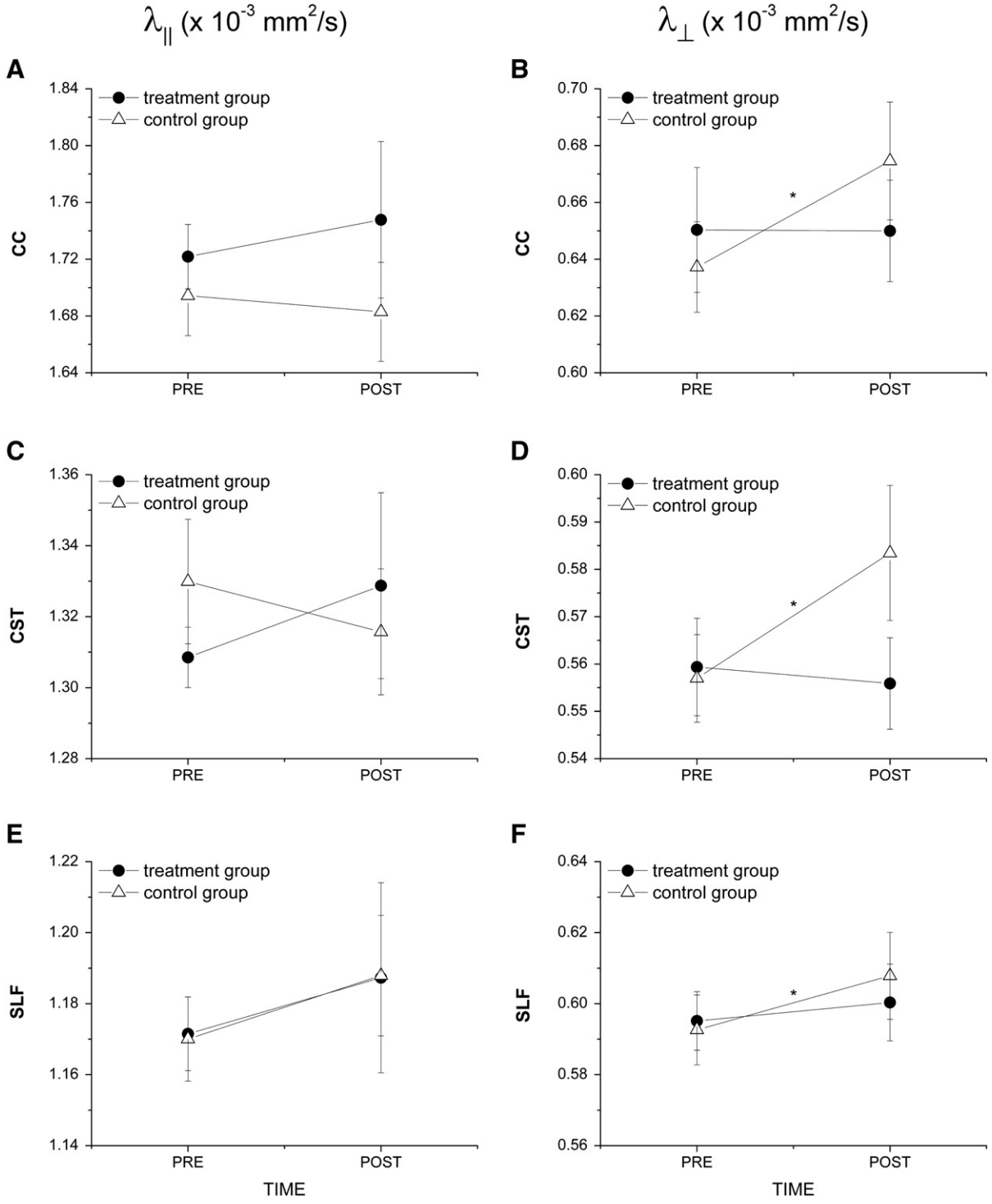

Fig. 5. Axial ($\lambda_{\parallel}$) and radial ($\lambda_{\perp}$) diffusivity values (mean ± s. e.) within the selected ROIs in the two groups of patients (treatment and control) before (PRE) and after (POST) the rehabilitation treatment. (A and D) Corpus callosum (CC). (B and E) Corticospinal tract (average on the left and right CST). (C and F) Superior longitudinal fasciculus (average on the left and right SLF). * indicates statistical significance. Please note that * in F refers to a significant effect of TIME in both groups.

No significant change in MD was observed after treatment in both groups (effect of TIME) (CC: $F(1,28) = 2.60$, $p = 0.12$; CST: $F(1,56) = 2.33$, $p = 0.13$; SLF: $F(1,56) = 3.59$, $p = 0.07$). This trend was similar in the two groups as indicated by the lack of TIME × GROUP interaction (CC: $F(1,28) = 0.49$, $p = 0.49$; CST: $F(1,56) = 0.56$, $p = 0.46$; SLF: $F(1,56) = 0.32$, $p = 0.58$).

Discussion

In this work we showed that a 2-month upper limb rehabilitation treatment including task-oriented exercises in patients with multiple sclerosis positively influenced motor behavior and impacted white matter architecture. Indeed, following this treatment white matter integrity

in the corpus callosum and corticospinal tracts was preserved, while it is generally affected by the disease course. In fact, in a control group of patients receiving only passive limb mobilization we observed a microstructural integrity worsening in these fiber bundles, although these patients significantly improved some aspects of their motor behavior.

Motor behavior

Both active and passive motor rehabilitation protocols induced an improvement in unimanual motor tasks. In details, the ARAT score significantly increased in both groups of PwMS; similarly, a significant improvement was observed in hand dexterity (i.e., reduction of the time occurring to perform the 9-HPT) and in grip strength in both groups. Further, finger movement opposition rate at maximal velocity significantly increased in all patients.

However, it should be noted that the positive effects on motor behavior obtained with both the rehabilitation protocols may have different explanations. One can refer to the stimulation of the upper limb proprioceptors and cutaneous receptors during both active and passive movements inducing a continuous updating and enhancement of the sensorimotor cortical representation of the treated limb. Indeed, even though passive mobilization is usually considered less robust than active motor tasks in rehabilitation, the involvement of M1 has been recently discussed also in passive protocols (Blatow et al., 2011). Furthermore, M1 has been shown to play an important role in the somatic perception of limb movements (Naito et al., 2002). Recently, it has been demonstrated that there is a contralateral M1 activation in a similar location with active and passive motor stimulation, but the passive task is sometimes associated with lower signals than the active one (Francis et al., 2009; Guzzetta et al., 2007; Reddy et al., 2001). Also, a more prominent increase in the activation of contralateral M1, corticospinal excitability and intracortical facilitation was found after training based on the performance of voluntary movements compared with passive training (Lotze et al., 2003). From all these findings, we cannot exclude that although passive movements have a lower influence on the sensorimotor areas than the active ones they can, in the same way, induce a positive training effect on motor behavior. Another explanation may deal with the effects of rehabilitation on muscle properties. At rest, the human muscle undergoes a significant progressive increase in stiffness (Hagbarth et al., 1985): in patients with upper limb motor impairment this increased stiffness can reduce the ability to correctly perform the motor tasks increasing the time occurring to accomplish the goal. It has been demonstrated that this stiffening can be reversed by active or passive movements (Lakie and Robson, 1988). The biophysical basis of this thixotropic process is likely to involve a long-term rearrangement of bonds between actin and myosin molecules and to be related to the presence of the short-range elastic component in the muscle (Hill, 1968). Therefore, thixotropy may explain the beneficial effects of limbering up before exercise and the efficacy of certain forms of physiotherapy, based on the repetition of passive or active movements, in the treatment of muscle stiffness (Lakie and Robson, 1988).

However, these two explanations are not contradictory and we could hypothesize that the observed effects can be due to a combination of the discussed processes.

Nevertheless, it should be considered that bimanual coordination was found to be preserved only in the treatment group while it worsened in the control group. In a previous work, we showed that IHI, an index of bimanual coordination, is significantly higher in PwMS than in healthy subjects indicating a deficit in bimanual coordination in these patients (Bonzano et al., 2008). In the present study, similar IHI values were observed in the two groups of patients at the time of enrollment revealing altered bimanual coordination in both the treatment and the control groups. Yet, in the treatment group IHI remained stable after the 2 months of treatment while significantly increased in the control group. This finding indicates that when patients are asked to perform high complexity tasks requiring the coordination of both limbs the typology of the rehabilitation treatment becomes important. We can hypothesize that performing task-oriented exercises with one or two limbs, as those administered to the treatment group, can have positive effects on motor behavior because they induce a higher activity of the brain areas involved in voluntary movements than passive movements, with a continuous exchange of sensorimotor information between homologous areas of the two cortical hemispheres. This last process has been demonstrated to be crucial in both bimanual coordination and the interhemispheric transfer of sensorimotor information during motor task performance or motor training (Bonzano et al., 2008, 2011a,b; Lenzi et al., 2007).

Regardless of treatment-induced changes in the upper limb motor behavior in both groups, no patient changed the baseline EDSS score after treatment. The lack of change in this score can be explained by the fact that EDSS is weighted toward the lower limb function (Kurtzke, 1983) and, independently of treatment, by the short observation period (i.e., 2 months).

White matter integrity

After 2 months of upper limb passive mobilization (i.e., control group), FA values in both the CC and CST (left and right tracts) were significantly lower than those measured at baseline and $\lambda_{\perp}$ significantly increased in both the CC and CST, indicating a WM damage progression in this group. On the other hand, no significant change in FA and $\lambda_{\perp}$ was observed in the treatment group in both the CC and CST, indicating a preservation of these WM fiber bundles. Further, no significant change in $\lambda_{\parallel}$ and MD was observed in the investigated ROIs in the treatment and the control groups.

The changes observed in FA and $\lambda_{\perp}$, and not in $\lambda_{\parallel}$ and MD, in the control group might suggest that the WM damage progression in these patients might be due to increased diffusivity of water molecules across WM fibers likely related to demyelination processes rather than to altered impedance of diffusivity along the tract as a consequence of axonal injury or loss (Budde et al., 2007; Nair et al., 2005; Song et al., 2003).

The bases of these findings can be derived from recent studies considering the effects of motor training in healthy subjects and animal models. In healthy subjects, learning a novel skill may be mediated by a multi-stage process (Dayan and Cohen, 2011): a rapid skill learning, which is facilitated by an increase in spine density, and consolidation and slow learning phases over long periods of training, which can be mediated by changes in other cellular processes such as angiogenesis, myelination or axonal remodeling (Thomas and Baker, 2013). However, the nature of the structural changes may be strongly influenced by the type of training task and the neuroanatomical substrate. In PwMS, we showed that a rehabilitation treatment including task-oriented exercises can preserve WM microstructure and potentially induce a slight but not significant trend to improvement (i.e., FA increase in the CST, see Fig. 4B). We might assume that the same treatment in a group of healthy subjects can have a stronger impact on WM as it has been shown to occur after motor training (Scholz et al., 2009). However, Morgen et al. (2004) found that when training the motor functions in PwMS cortical reorganization of sensorimotor networks can occur, but on a lesser scale than in healthy subjects. The reduced cortical reorganization and the progression of the disease can explain why we observed only a preservation of WM integrity and not a considerable improvement. Interestingly, Rossi et al. (2009) found that in mice with myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE), a model of MS, exercise was able to contrast dendritic spine loss induced by EAE in striatal neurons.

In general, the DTI measurements could reflect changes also within plaques (we did not create a lesion mask to exclude these areas from the DTI analysis, thus the DTI measurements can include both plaques and normal-appearing white matter). However, the only two patients developing an enlarging or a new T2 lesion in the analyzed ROIs after

treatment showed a trend in DTI parameters similar to the other patients belonging to the same group (treatment and control group, respectively). Indeed, it should be considered that T2 hyperintensities are not specific for the underlying pathological process, since inflammation, demyelination, gliosis, edema, and axonal loss may increase the signal intensity, without any specific pattern (Bruck et al., 1997).

Recently, an interesting longitudinal study based on DTI in MS (Harrison et al., 2011) showed significant changes in white matter structures over time and in particular in the corpus callosum. The FA changes found in this work are lower than those observed in our control group; however, the authors underlined, as possible confound in their analysis, that some patients taking disease-modifying drugs changed the therapy during the course of the study. Also, their inclusion criteria allowed MRI scans in all the patients who did not take corticosteroid within 30 days from the DTI evaluation. All these conditions might have affected the results by reducing the absolute change over time. Conversely, in our work, the two groups were matched for MS phenotype, EDSS, disease duration, disease-modifying therapy and time from last relapse (see Table 1). Further, although some patients were taking disease-modifying drugs all of them did not change therapy in the 3 months preceding the enrollment and there was no therapeutic change during the study. All the patients did not use corticosteroid since their last relapse, and this occurred more than 3 months before the study, as from inclusion criteria (indeed, 8 out of 15 patients of the control group had the last relapse more than 12 months before the beginning of the study). In addition, we should take into account that in the control group, as in the treatment group, there were secondary progressive PwMS who can have a progressive deterioration (Cassol et al., 2004) augmenting the averaged damage progression of the control group.

Finally, we cannot exclude that passive limb mobilization could accelerate disease progression or negatively impact white matter integrity. This might have important consequences in the field of neurorehabilitation. Indeed, it has been already demonstrated that passive limb mobilizations and task-specific exercises have different effects on functional plasticity in the sensorimotor cortex (Hubbard et al., 2009) and it should be very interesting to better understand if this might differently impact the neural structures. Particularly, repetition alone, without usefulness or meaning in terms of function, could be not enough to produce increased motor cortical representations; on the other hand task-specific training regimens could produce cortical reorganization and associated, meaningful functional improvements (Bayona et al., 2005). Recently, in an elegant review Doron and Gazzaniga (2008) proposed this question: "Is the callosal microstructure shaped by the strategies of the brain, vice-versa, or does it result from interplay of the two?" We might assume that during a training based on task-oriented exercises different non-motor neural pathways located in the frontal, parietal and posterior cortical areas are active. Therefore, in this condition the majority of the callosal fibers, and not only the sensorimotor ones as in a passive mobilization treatment, could have a role in allowing the interhemispheric communication and at the same time undergo structural plasticity processes.

Further, we demonstrated that the type of training task cannot have a general impact on brain architecture, as it is able to influence only specific structures. Indeed, we did not find a significant positive effect of training on the SLF. On the other hand, we found a significant increase of $\lambda_{\perp}$ in the SLF with respect to baseline in both groups, likely due to a demyelination process as effect of the disease. The main reason for the lack of treatment effects on the SLF might deal with its involvement also in other functions related to cognitive processes (Bonzano et al., 2009; Genova et al., 2013), thus a combined rehabilitation approach including also cognitive domains might be more efficient on these fiber bundles. These findings strongly support the idea that the beneficial effects of a rehabilitation treatment are task-dependent and selective in their target. This last suggestion assumes relevant significance towards the implementation of tailored rehabilitative approaches, according to which a personalized treatment should be defined for the single patient on the bases of the specific functional aspects to be rehabilitated and the brain structures damaged by the disease to be preserved.

Conclusions

The commonly adopted tests showed an improvement in motor performance in both the treatment and the control group. Conversely, bimanual coordination and WM integrity in the corpus callosum and corticospinal fiber bundles, generally affected by the disease, were preserved only in the treatment group. This result points out to the need to administer, when possible, a rehabilitation treatment based on voluntary movements since it seems to be more efficient than passive mobilization. Further, we can make the hypothesis that life style and experiences might influence the clinical course of inflammatory neurodegenerative diseases with effects on WM architecture, as occurs when PwMS undergo aerobic exercise training (Prakash et al., 2010).

Finally, we can also suggest that the choice of the outcomes to evaluate the efficacy of a rehabilitation treatment is crucial. Indeed, diverse treatments can influence the neuromuscular system at different levels also activating, in some cases, compensatory mechanisms but showing similar changes in the evaluated outcomes. Therefore, we can propose that in neurorehabilitation, where a successful treatment has to influence both behavior and neural structures, it should be desirable to combine the analysis of behavioral data with the analysis of brain structure and function to assess more completely the effects of a treatment.

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Conflict of interest

The authors have no conflict of interest to disclose.

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